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Marine resources-based metabolites in nanoparticles synthesis and their cutting-edge applications in microbial sciences

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Abstract
Marine resources are treasure for the research, since they can synthesize a group of secondary metabolites associated with promising biological activities. Nearly all marine habitats, from the deep sea to surface waters, have been discovered to contain bioactive metabolites. Algae, Fungi, Bacteria etc are the huge source of such bioactive compounds. But utilisation of such compounds still a topic of research as they are not easily absorbable in human bloodstream. These compounds act as reducing agent and forms conjugate with metal oxide, silver, gold, chitosan, zinc and etc. The objective of this chapter was to make readers understand about the marine metabolites including phenolic, flavonoid and carbohydrate which shows significant antimicrobial activity against differential microbes and their efficiency in synthesizing nanoparticles.

Keywords: Food biotechnology; antimicrobial; metabolites; marine resources; pharmaceutical; nanotechnology

Introduction
Bioactive compounds from algae, bacteria, and plants are Secondary metabolites produced by them for defence mechanism. Phenolic compounds are among the bioactive substances that are abundant in the marine environment. One of the most frequently accepted ideas explaining why marine plant (seaweed) tissues develop and accumulate phenolic compounds is that these substances are produced as a defensive mechanism against biotic and abiotic stimuli. There are various theories explaining why this is the case. It is vital for Seaweeds (macroalgae) to create defence mechanisms throughout their metabolic pathways that protect them against the environmental stress and biological agents like UV protectant, anti-herbivory, and antioxidants in order to adapt and survive in a very competitive and difficult marine environment [1]. Distinct genera of seaweed have different phenolic chemical types and compositions based on their habitat. Brown, green, and red seaweed are few examples that are used to separate and describe several phenolic component types [2]. These bioactive compounds shows several biological properties such as antioxidants [3], anti-inflammation [4], antimicrobial [5], anticoagulant [6], anticancer agents [7], antidiabetic [8], and etc. However, little is known about how these metabolites are absorbed, distributed, and eliminated from individuals. The amount of a bioactive molecule that can enter the bloodstream is known as bioavailability. The primary issue that must be taken into account when creating functional foods is the bioavailability of these metabolites. After consumption of metabolites through our food meals, these must pass through intestines, stomach, and mouth to enter the circulation; such is poor penetration, uncontrolled release in the stomach and small intestine, and degradation are the main barriers for the absorption of these from the intestine epithelium to the bloodstream [9]. Nanocarriers have been shown to be a promising choice for enhancing the bioavailability of these metabolites. That could be the possible solution to overcome the bioavailability issue [9].
The aim of this chapter is to make readers understand the antimicrobial properties of marine metabolites against pathogenic bacteria's and the role of metabolites in nanotechnology. Such knowledge is important for the development of antimicrobial compounds for preservation of health-promoting functional foods and for several biological application.

Metabolites in marine resources
Phenolics
Phenolic compounds has significant contribution to the growth and survival of organisms, as

well as their assistance in the defence against infections and predators, they are found in a huge range of terrestrial and marine plants. Following the pentose phosphate, shikimate, or phenylpropanoid routes, these substances can be produced. Lignan is a phenolic molecule that is created when p-coumaryl alcohol and monolignols combine to form a dimer or oligomer. Contrary to popular belief, it has also been found in calcified intertidal red seaweed *Calliarthron cheilosporioides* Manza which was previously assumed to only exist in terrestrial plants [10]. Algae are a diverse and complicated class of organisms distinguished by their ability to photosynthesise and their uncomplicated reproductive system. They are categorised into four classes based on the colours they contain: Cyanophyta (blue-green algae), Rhodophyta (red algae), Phaeophyta (brown algae), and Chlorophyta (green algae). As a result of their varied habitats and exposure to harsh climatic circumstances, marine algae create a large range of physiologically active metabolites that are not present in any other species. As chemical defence mechanisms, these metabolites help algae survive in conditions with intense competition [11].

Tannins, a common family of phenolic compounds found in many terrestrial plants, have drawn a lot of attention in recent years due to their strong antioxidant capacity. Hydrolyzable tannins also known as pyrogallol-type tannins, basically derived from simple phenolic acids such as gallic or ellagic acid, are molecules with a polyol (generally D-glucose) as a central core. These carbohydrates' hydroxyl groups undergo partial or complete esterification with phenolic groups like gallic acid (gallotannins) or ellagic acid (ellagitannins). These tannins produce gallic or ellagic acid when heated with sulfuric or hydrochloric acid. They can be found in some varieties of green algae and are typical in angiosperms [12]. In Western nations, algae are an underappreciated source of phenolic compounds since they are typically seen as marine garbage. Their consumption is expanding as a result of current diet trends based on functional foods. *Bifurcaria birfurcata has* 9.6 mg PGE/g of phenolic content followed by *Chlamydomonas reinhardtii* 150 mg GAE/g, *Chlorella* spp. 58.2 mg GAE/g, *Enteromorpha intestinalis* 0.03 mg GAE/g, *Fucus* spp. 28.2–204.2 mg PGE/g, *Himanthalia elongate* 151.3 mg GAE/g, *Nannochloropsis* spp. 33.2 mg GAE/g, *Padina pavonica* 20.3 mg GAE/g, *Phormidium valderianum* 0.97 mg GAE/g, and Spirulina platensis 2.4–5.0 mg GAE/g [13-19]. From the ethanol and dichloromethane extracts of *P. boryana* and *A. spicifera*, respectively, Hassan *et al*. isolated two polyphenolic substances known as ellagic acid and velutin [20]. After being subjected to HPLC anlysis, several phenolic components, including ellagic acid and gallic acid, which had the highest amounts of 19.05 and 18.36 µg/mL, respectively, were found in *Amphiroa anceps* extract after being subjected to HPLC analysis [21].

Flavonoids

In the polyphenol family, there are several bioactive natural chemicals, but flavonoids are the most numerous and diversified group [22]. Numerous plant taxa, including bryophytes (liverworts and mosses), ferns, gymnosperms, and angiosperms have produced more than 4,000 flavonoids. The most primitive plant species that contain flavonoids are green algae [23]. Research on the production of flavonoids in plants is widespread. Because algae have a long evolutionary history, one can speculate that their metabolic pathways for flavonoid production are distinct from those of higher plants. However, the discovery of caffeine in *Chlamydomonas eugametos* disproved the aforementioned hypothesis [24]. According to a study by Goiris *et al*., microalgae contain many flavonoids and intermediaries that are involved in the formation of flavonoids. Phloretin and dihydrochalcone, which were discovered in *Diacronema lutheria*, may be products of the intermediates in the production of flavonoids [25].

The majority of woody plants, as well as red wine, tea, and cocoa beans, contain flavonoid-based condensed tannins, polyflavonoid tannins, catechol-type tannins, pyrocatecollic type tannins, nonhydrolyzable tannins, or flavolans [26]. They produced through the biosynthesis of catechins and flavins. Over half of the 8000 naturally occurring phenolic chemicals are flavonoids, which make up the biggest group of plant phenolics [27]. There have been several studies on the flavonoids found in terrestrial plants, but less is known about the flavonoids found in algae. A recent analysis of the distribution of flavonoids in six Chlorophyta, eleven Phaeophyta, and ten Rhodophyta species of marine algae revealed that their flavonoid profiles are completely dissimilar to those of vegetables and fruits. Macroalgae are abundant sources of catechins, flavones, and flavonols, according to other studies [28]. Algae have not been identified to contain anthocyanins and flavones, in contrast to terrestrial plants [29]. In contrast to hydrolyzable or condensed tannins, phlorotannins are oligomers of phloroglucinol and are only present in brown sea algae [30]. There are two different forms of the benzenetriol 1,3,5-trihydroxybenzene also known as phloroglucinol; one is phenol-like, and the other is 1,3,5-cyclohexanetrione (phloroglucin), which is ketone-like. Additionally, the phytochemical study of *Amphiroa anceps* revealed the presence of flavonoids, with catechin having the greatest content (12.45 g/mL) [21].

Carbohydrates

Carbohydrates are significant metabolites in marine life, as they exhibit antioxidant and immunity boosting properties. For example, Trehalose is a disaccharide found in seaweed and shrimp that has an anti-aging effect through regulating the Nrf2 and insulin signalling pathways. most naturally occurring carbohydrates found in marine organisms are polysaccharides, with a small number being mono or oligosaccharides [31].

Alginate, fucoidan, and laminarin are the three primary forms of soluble dietary fibre polysaccharides found in brown algae. Alginate is made up of polymannuronic acid, polyguluronic acid, and a linear synthesis of both of these acids. It exists in a variety of forms, including acid and salt, and is regarded as a crucial component of the cell wall. Fucoidan has an extremely broad and intricate structure, in contrast to alginate and laminaran. It is a sulfated polysaccharide that contains various monosaccharides along with fucose sugar. Like galactose, xylose, glucose, glucuronic acid, and mannose [32].

Agar, alginate, carrageenan, and fucoidan like Polysaccharides show a variety of physiological properties it could be one of the reasons that they are widely used in food, agriculture, and health. Nevertheless, their limited application is hampered by their weak solubility and low absorption. Marine oligosaccharides, which are breakdown products of those polysaccharides, have garnered a lot of interest due to their clear biological activity, improved solubility, and greater bioavailability [33].

In addition, a major portion of hydrocolloids, including agar and carrageenan from Rhodophyta, are obtained from algae. These hydrocolloids are widely used as thickeners and gelling agents in the food industry and have a large market. In 2009, their sales with a market value of USD 1018 million [34]. Red seaweed has the ability to digest Floridian starch, which is a type of amyl that is similar to glucose. Oceanic brown algae come in a variety of sizes and shapes and are a type of multicellular algae. Brown algae have a high concentration of carbohydrates, which make up more than half of their dry biomass. Food and alginate extraction is one of the reasons why brown algae is being farmed enormously [35]. Omega-3 fatty acids, chitin, chitosan, algal components, carotenoids, and other bioactive chemicals are a few examples of high value-added substances with nutraceutical potential that can be used as functional additives. Nowadays, polysaccharides like chitin and chitosan are becoming more and more popular [36].

Role of marine metabolites in nanoparticle synthesis

The advancement of numerous industries, including food, medicines, nanomedicine, and environmental trends, is supported by current marine biology research and the marine biology revolution [37]. Oceans cover about 75 percent of the earth's surface, wherein around 2.2 million unique species have been analysed [38, 39]. The ocean contains a large quantity of marine-derived substances having numerous human-valued uses, such as antibacterial substances [40]. In the marine ecosystem, there are roughly 30,000 biologically active compounds with a wide range of uses [41]. Various antibacterial, antifungal, and antiviral chemicals are currently made possible by the marine environment. Potential sources for fighting infectious disorders include seaweeds, bacteria, and fungi [42]. There has been a lot of interest in marine-based nanoparticles made from a range of marine sources, such as bacteria, fungi, marine plants, and seaweeds [43]. *Spirulina platensis*, *Ulva lactuca*, and *Sargassum muticum* are examples of algae that are viewed as prospective biocatalysts for the synthesis of various types of nanoparticles because of their rapid cell growth rates, high stress tolerance, and quantity of physiologically active chemicals [44].

Both intracellular and extracellular inorganic secondary metabolites produced by marine bacteria, fungus, and algae convert metal ions to generate nanoparticles. Nanoparticles are created inside of cells by trapping the positively charged metal ions on the surface of the cell wall or/and in the cytoplasm that contains negatively charged groups of enzymes or proteins. Different types of nanoparticles are created as a result of the reduced metal ions being confined into tiny nuclei [45]. For instance, it has been shown that alkalotolerant actinomycetes, *Rhodococcus* spp., gold nanoparticle production was observed in the cytoplasmic membrane and on the surface of mycelia. As a result, the cytoplasmic membrane had more gold nanoparticles than the cell wall, demonstrating that the interaction of the enzymes on the cytoplasmic membrane is what causes the formation of the gold nanoparticles [46]. Due to the presence of enzymes on the cell wall membrane, silver nanoparticles were synthesized when biomass from the *Verticillium* fungus species was exposed to silver ions below the surface of the cell wall [47]. In the case of *Tetraselmis kochinensis* algae, into HAuCl4 solution, the biomass was added and monitored for the synthesis of gold nanoparticles intracellularly. There were more gold nanoparticles on the cell wall than the cytoplasmic membrane. The cytoplasmic membrane and cell wall enzymes were responsible for the creation of the gold nanoparticles [48].

On the other hand, microbial surface proteins and enzyme secretion are necessary for the extracellular creation of metallic nanoparticles. Proteins and DNA are examples of macromolecules that are described as assemblies of nanoparticles [49]. The necessity of nitrate reductase for the reduction of metal ions has been shown. Similar to this, it has been discovered that the bacterium *Rhodopseudomonas capsulata* exhibits NADPH-dependent nitrate reductase activity for producing gold nanoparticles from $AgNO_3$ [50]. When *R. capsulata* secretes cofactor NADH to NADH-dependent enzyme, the electron is transferred from NADH to NADH-dependent reductase as an electron carrier. Finally, the electron is taken in by the gold ions, who then transform it into gold nanoparticles. Using an algae *Chlorella vulgarris*, Ferreira and colleagues created extracellular silver chloride nanoparticles [51]. Silver nitrate was converted by the microalgae into silver chloride nanoparticles.

Terpenes, acetogenin, pure aromatic compounds, and polyphenolic substances found in marine algae, including phloroglucinol, eckol, phlorofucofuroeckol A, fucodiphlorethol G, 7-phloroeckol, 6,60-bieckol, and dieckol, all function as reducing agents during the nanoparticle formation process [52, 53]. Gold nanoparticles have been synthesized using *Sargassum crassifolium*, a marine macroalgae having a range of polysaccharides and sterols [54]. Using *Cystoseira trinodis*, CuO nanoparticles of about 7 nm in size have been bioengineered [55]. Aluminum oxide nanoparticles with a size of around 20 nm were created using *Sargassum ilicifolium*. There have been reports of the production of gold nanoparticles by a number of algae strains, including *Turbinaria conoides*, *Laminaria japonica*, *Acanthophora spicifera, and Sargassum tenerrimum* [56]. The application of *Spriruna plantensis* in the synthesis of new core (Au)-shell (Ag) nanoparticles has also been investigated. Because of its high viscosity, ability to gel, and biocompatibility, carrageenan, a high-molecular-weight, water-soluble, and sulfated polysaccharide isolated from numerous species of red algae, has been widely used in the pharmaceutical, medical, and food industries [57]. Kappa-carrageenan wrapped zinc-oxide nanoparticles (KC-ZnONPs) with antibacterial and antibiofilm activities against methicillin-resistant *S. aureus* (MRSA) were by Vijayakumar *et al*. in 2020 [58].

It has been documented that marine bacteria can produce several kinds of metallic nanoparticles. The production of silver nanoparticles by *Pseudomonas stutzeri* AG259 has been documented whereby the produced particles are collected in the periplasm [59]. However, the extracellular synthesis of gold nanoparticles utilising the cell-free Bacillus marisflavi extract has been described [60]. Another study demonstrates that thermophilic *Bacillus sp.* produced extracellular silver nanoparticles when combined with the silver nitrate solution and incubated at 27 and 50 °C for 48 hours in the dark [61]. Silver nanoparticles are synthesized when *Nocardiopsis sp*. MBRC-1 culture supernatant is inoculated with silver nitrate solution and cultured in the dark at 30 °C for 96 hrs at (pH 7.0) [62]. Gold nanoparticles were created during the intracellular synthesis, which involved suspending *Rhodococcus sp.* biomass in a HAuCl4 solution and incubating it for 24 hrs at 27 °C and 200 rpm. The membrane and cell wall of *Rhodococcus spcytoplasmic* contained the synthesized gold nanoparticles [63].

There have been reports of both intracellular and extracellular metal nanoparticle production in a variety of marine fungus. Compared to bacteria, fungi are better able to produce metallic nanoparticles since they exude extracellular enzymes that enable handling biomass easier [64]. *Candida albicans'* cytosolic extract was used extracellularly to produce gold nanoparticles [65]. Additionally, it has been reported that *Penicillium fellutanum* and *Phoma glomerata* are used in the extracellular synthesis of silver nanoparticles [66]. Gold nanoparticles have recently been produced intracellularly using *Penicillium chrysogenum*. Gold nanoparticles were synthesized after 72 hours of incubation at 30 °C with the active biomass of *P. chrysogenum* inoculated in HAuCl4 solution [67]. It has been reported that the fungi *Candida glabrata* and *Schizosaccharomyces pombe* produce cadmium sulphide nanoparticles intracellularly. Since the cadmium sulphide nanoparticles' concentration is dependent on the type of cell, they were synthesized by lysis of cells [68].

Antimicrobial Activity of Marine Resources-Based Metabolites against Harmful Pathogens

According to estimates, marine bacteria produce around 50,000 bioactive secondary metabolites. Among the diverse marine microorganisms, marine bacteria create secondary metabolites that have a variety of biological properties, including possible antibacterial properties [69]. Among the various marine bacteria phyla researched, Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, Planctomycetes, and Proteobacteria appear to be the frequently primary producers of antimicrobial chemicals [70].

Gram-positive bacteria called actinobacteria are renowned for producing a wide range of valuable secondary metabolites. The abundance of actinobacteria in maritime environments has a crucial ecological function in the reprocessing of resistant biomaterials and the production of various biological chemicals with medicinal uses [71]. *Streptomyces sp*. 1492's antibacterial effectiveness was uncovered in 2021 by Quinn G. *et al*. against bacterial diseases such *E. faecium*, *S. aureus*, and *A. baumannii* [4]. They additionally demonstrated that the chlorocatechelins, a new siderophores with chlorinated catecholate complexes and acylguanidine structure isolated from *Streptomyces sp*., suppressed the growth of a wide variety of bacterial pathogens [72]. Additionally, a brand-new strain of *Streptomyces sp*. MUSC 125 was found and isolated from mangrove soil on Peninsular Malaysia's east coast. This strain is capable of generating the broad-spectrum antibiotic molecule bacitracin A, which is effective against *S. aureus* ATCC BAA-44 [73]. Other novel bioactive substances, such as phenylacetic acid and indole-3-lactic acid, that were isolated from Streptomyces CTF9's fermentation broth had potent antifungal activity against *Candida albicans* [74].

Marine Secondary metabolites produced by cyanobacteria are a rich source of previously well-reported pharmacological activity, such as antibacterial, antiviral, antifungal, anticancer, and antiplasmodium effects [75]. The unique ambiguine-K and *M isonitrile* isolated from marine cyanobacterium *Fischerella ambigua* (UTEX 1903) has shown good antibacterial activity against *Mycobacterium tuberculosis* with MIC values of 6.6 and 7.5 µM, respectively [76]. Alkylphenols and anaephenes A–C with mild growth inhibition against *S. aureus* were obtained from the cyanobacterium *Hormoscilla* sp. [77]. The anaephenes A, B, and C, at concentrations of 22, 6.1, and 22 µg/mL, respectively, completely prevented the visible development of *S. aureus*. Aqueous extracts of *Spirulina platensis* and *Nostoc ellipsosporum* include a number of polysaccharides with antiviral properties. Calcium spirulan, a sulfated polysaccharide produced from *Spirilina plantensis*, was found to inhibit the replication of measles, HIV-1, herpes simplex virus-1 (HSV-1), mumps, polio, and influenza A viruses when tested on several cell lines [78].

The phylum Firmicutes contains Gram-positive bacteria. The most important member of a group of Firmicutes is Bacillus. *Bacillus sp*. may grow swiftly in liquid culture and is temperature-tolerant. Typically, marine sand samples and other marine ecosystems contain Bacillus species [79]. A unique oxatetracyclo ketone antimicrobial complex isolated from *B. stercoris* MBTDCMFRI Ba37 strain showed growth inhibition of aquatic bacterial, *Aeromonas* and *Vibrio* [80]. Micrococcin, discovered by Wang *et al*. in 2021, is a member of the thiopeptide class of antibiotics isolated from marine *B. stratosphericus* and exhibits antibacterial activity against gram-positive bacterial infections [81].

The most diverse phylum of Gram-negative bacteria is known as protozoa. The phyla of marine bacteria producing biologically active compounds with antibacterial, antiviral, antibiofilm, antifouling, and anticancer effects are frequently attributed to proteobacteria [82]. It has been discovered that the antibiotic compound thiomarinol is produced by *Pseudoalteromonas species* that have been isolated from marine invertebrates and seaweed [83]. Proteobacteria discovered by Dat *et al*. (2021) that produce macrolactin A and macrolactin H as the main bioactive chemicals and have potent antibacterial properties against a variety of pathogenic organisms [84].

Planctomycetes is a different phylum of bacteria that can be found in freshwater, soil, and marine settings. Although it occurs infrequently, it can live freely or attach to both biotic and abiotic surfaces [85]. They are capable of producing antimicrobial substances such polyketides, nonribosomal peptides, terpenoids, and bacteriocins, according to research using mass spectrometry. [86]. The generating strain, *S. maiorica* Mal15, and the co-occurring marine bacterial species' growth and biofilm could both be reduced by the tyrosine chemical stieleriacine, which was isolated from *Stielera maiorica* Mall5 [87].

Conclusion

The increasing population is a global concern resulting in supply of health product and subject to healthy life. Marine resources will become one of the solution of this issue. Marine algae, microbes are the rich source of these metabolites which can easily make available the health supplements to the community. Phenolic compounds, flavonoids and carbohydrate play major role as such health supplements. The extraction techniques and their purification still needs some attention for their biorefineries. These bioactive materials can also be useful in food packaging and other antimicrobial applications.

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